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I. Status of the Claims

Claims 16-21 have been examined and stand rejected. Claims 16-21 are rejected under 35 U.S.C. §112, second paragraph; claim 21 is rejected under 35 U.S.C. §112, first paragraph; and claim 21 is also rejected under the judicially-created doctrine of obviousness-type double-patenting. The detailed basis for the rejections, and applicants' response thereto, are set out below.

II. Rejection Under 35 U.S.C. §112, Second Paragraph

Claims 16-21 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 16 and 17 are specifically objected to by Examiner, and applicants respond accordingly below.

Claim 16 includes the phrase "in the spatial region" to describe positions of key amino acids, relative to each other, within an FcRn binding protein or peptide. Examiner asserts this phrase is unclear, questioning whether it refers to the linear, primary amino acid sequence or to a three-dimensional feature of the structure itself. The Action, page 2. Applicants traverse the rejection regarding this purported ambiguity.

In various portions of the specification, applicants define the metes and bounds of "spatial region." The specification, with certain Examples, show that second amino acids may potentially encompass elements of both linear and three-dimensional space. Said second amino acids are to be chosen in light of their proximity to the first amino acid; as a consequence, said second amino acid may or may not be in linear proximity to the first amino acid so long as if it is nearby. The specification alludes to as much, as would be understood to one of ordinary skill in the art.

Beginning with page 5, line 11 of the specification, applicants first use the phrase "in the ***spatial vicinity*** of the direct interaction [of a first amino acid and FcRn]" to describe the positioning of the side chains of one or more second amino acids relative to the identified first amino acid (emphasis added). Further, "In preferred embodiments, the increased half-life Fc-hinge mutants will have changes in certain amino acids between about residue 252 and about residue 436, which have been discovered to form, or be in ***close proximity*** *to*, the 'catabolic control site.'" Specification at page 6, lines 1-4 (emphasis added). Page 22, lines 18-23, 26-27, and page 23, lines 1-5 of the specification first use the exact phrase of interest, and suggested amino acids—both specific and within a range—follow:

> The invention also encompasses a method of making an antibody with an increased serum half life comprising identifying a first amino acid in an IgG hinge region that is suspected of being directly involved in FcRn binding, identifying one or more second amino acids wherein each of said second amino acids is in the ***spatial region*** of said first amino acid, and wherein the side chain of said second amino acid is exposed to solvent in the native antibody.... In the practice of this method, the first amino acid may be amino acid number 253, 310, 435 or 436 of the Fc fragment, and the second or secondary amino acid may be amino acid number 252, 254, 256, 309 or 315 in the CH2 domain or 433 or 434 in the CH3 domain. In certain broad aspects, the invention may be described as a composition comprising an Fc fragment comprising the fragment from about amino acid 250 to about amino acid 440 of an IgG antibody...

(emphasis added) This section highlights the fact that some of the enumerated amino acid positions are indeed linearly sequential, but not all.

While portions of the specification may suggest that secondary amino acids linearly proximate to the first amino acid are claimed (*e.g.*, "Also random mutagenesis of residues ***flanking*** these key amino acids, followed by selection, may yield an Fc fragment with increased half life" (specification at page 43, lines 12-14 (emphasis added); see also Example 9, pages 112-113), later descriptions within the specification show the significance of the cross-space or three-dimensional

effects of these second amino acids: "For example, mutating hydrophilic residues that are essential to maintain the tertiary, or three-dimensional, structure of the protein to large hydrophobic residues would probably not be desirable since such mutations may destabilize the antibody and not extend the half life of the molecule." Specification at page 49, line 26 to page 50, lines 1-3. Taken together, these portions of the specification indicate that one may choose to mutate a secondary amino acid, relative to the first amino acid, based on its location in the primary amino acid sequence, ***or*** based on its location in three-dimensional space. The term "spatial region" therefore encompasses both these possibilities, and the phrase is adequately supported in the specification.

This duality is illustrated in Example 10, pages 118-119:

> Previous work has indicated that Ile253, His310, Asn434, His435 and His436 play a role, either directly or indirectly, in binding to FcRn (Kim et al., 1994a; 1994b; Medesan et al., 1997 and Example 9). Residues ***flanking*** these key residues, *and* have side chains that, ***from the X-ray structure*** of human IgG1 (Deisenhorfer, 1981), are most likely exposed *in the vicinity* of the CH2-CH3 domain interface were selected for random mutagenesis.... As His433 and Asn434 are highly exposed on a loop protruding from the CH3 domain (Deisenhofer, 1981), there are few ***flanking*** residues that would be preferred candidates for mutagenesis.

(emphasis added) Thus, while the phrase is not defined explicitly in the specification, one can see that applicants have sufficiently described the nature of the term "spatial region" with respect to the positioning of chosen secondary amino acids relative to identified first amino acid. The Examiner has also referred to M.P.E.P. §2173.05(b) (8th Ed.) concerning Relative Terminology: "The fact that claim language, including terms of degree, may not be precise, does not automatically render the claim indefinite under 35 U.S.C. 112, second paragraph."

Finally, one of ordinary skill in the art would understand the metes and bounds of "spatial region" from two separate angles. First, as outlined above, "spatial region" is described in the specification. Second, parameters of the phrase would be common knowledge to one of ordinary

skill in the art: one would only want to mutate secondary amino acids capable of altering a chosen system. Such amino acids would most likely be those in close physical space to the identified first amino acid. As such, a secondary amino acid candidate would most likely be linearly proximate to the first amino acid, or nearby in terms of the system's tertiary structure. Hence, "spatial region" is sufficiently defined for one of ordinary skill in the art. Applicants therefore respectfully request reconsideration and withdrawal of the rejection.

Claim 17 is also rejected by Examiner because of the purported uncertainty of the phrase "the step of isolating said antibody" with respect to claim 16, upon which claim 17 depends. Examiner states, "Applicant must clarify in accord with what the specification teaches and point out the location in the specification that supports any new recitations." The Action, page 2. Applicants have amended claim 17 such that it now reads, "The method of claim 16, further comprising the step of isolating the identified mutant antibody." This is believed to address the examiner's concerns.

To address the question of where the phrased step fits into claim 16, applicants believe that the amended claim provides sufficient clarity for one of ordinary skill in the art. Further, the amended claim is supported by the specification. After describing the method for making an antibody with an increased serum half life, applicants note on page 22 of the specification, lines 25-26: "This method may further comprise the step of isolating the antibody." A natural reading of this section would lead one of ordinary skill in the art to assume that the isolation step must follow behind the final step of the method outlined in the sentences before: one must have the mutant antibody made by the claimed method (of claim 16, specifically) before one can isolate the mutant antibody.

One of ordinary skill in the art would also understand the phrase in question to refer to the isolation of a mutant antibody from other members of the generated library of mutants. As such, the isolation step is effectively a purification step, and the specification indicates as much. Pages 30, lines 10-14 and page 42, lines 18-19 of the specification address the isolation process generally, while specifics are addressed on page 20, lines 1-3 and Example 4, page 74.

Applicants request acceptance of amended claim 17 as written above, and reconsideration and withdrawal of the rejection is respectfully requested.

III. Rejection Under 35 U.S.C. §112, First Paragraph

Examiner rejects claim 21 under 35 U.S.C. §112, first paragraph, asserting that "applicant was not in possession of the genus of antibodies having an increased serum half-life, when obtained by the process of base claim 16." The Action, page 2. Examiner argues that "***The product must be defined by structural features*** which would distinguish it from other antibodies which would not fall within the genus." The Action, page 3 (emphasis added). Applicants respectfully traverse this argument.

Claim 21 is a product-by-process claim, as Examiner duly notes. The Action, page 4. Product-by-process claims are ***not*** the same as product claims. "A product-by-process claim, which is a product claim that defines the claimed product in terms of the process by which it is made, is proper." M.P.E.P. §2173.05(p) (8th Ed.). Product claims, by contrast, require "'precise definition[s], such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Univ. of Calif. v. Eli Lilly,* 43 U.S.P.Q.2d 1398, 1405 (Fed. Cir. 1997), quoting *Fiers v. Sugano,* 25 U.S.P.Q.2d 1601, 1606 (Fed. Cir. 1993). *Lilly* also distinguishes as well as supports the validity of the two types of claims: "[I]n addition to being

claimable by structure or physical properties, a chemical material can be claimed by means of a process." 25 U.S.P.Q.2d at 1605, citing *Amgen Inc. v. Chugai Pharmaceutical Co.*, 18 U.S.P.Q.2d 1016 (Fed. Cir. 1991). If products such as the antibody claimed in claim 21 were required to be defined by structural or formulaic factors, product-by-process claims would be *per se* invalid. Because the M.P.E.P. contemplates such claims (§2173.05(p)), the definition required by the Examiner is improper.

Thus, the present claim can be distinguished from *Fiers* and *Lilly* by virtue of the types of claims involved: the two cited cases concern product claims, not product-by-process claims. The patent in *Fiers* regarded a disputed product claim, although part of Fiers' argument rested in (unclaimed) methodology behind the claim. 25 U.S.P.Q.2d at 1605. But Fiers' claim was ***not*** a product-by-process claim, and is hence distinguishable from claim 21. The patent in *Lilly* did discuss methodology within the specification in relation to claimed products, but the claims did ***not*** recite any product-by-process limitations. 43 U.S.P.Q.2d at 1405. Because of the differences in the nature of the relevant claims, Examiner erroneously relied on these two cases for supporting a 35 U.S.C. §112, first paragraph rejection of claim 17.

Because the nature of the product-by-process claim of claim 21 is separate and distinct from product claims addressed in *Fiers* and *Lilly*, applicants respectfully request that Examiner's 35 U.S.C. §112, first paragraph rejection be withdrawn.

IV. Rejection for Obviousness-Type Double-Patenting

Claim 21 is rejected under the judicially-created doctrine of obviousness-type double-patenting. Without acquiescing to this rejection, a terminal disclaimer will be provided at such time as all the claims are otherwise allowable.

V. Conclusion

In light of the foregoing, applicants respectfully submit that all claims are in condition for allowance, and an early notification to that effect is earnestly solicited. Examiner is invited to contact the undersigned at (512) 536-3184 with any questions, comments or suggestions relating to the referenced patent application.

Please date stamp and return the enclosed postcard as evidence of receipt.

Respectfully submitted,

Reg. No. 42,608

For: Steven L. Highlander, Esq.
Reg. No. 37,642
Attorney for Applicants

FULBRIGHT & JAWORSKI L.L.P.
600 Congress Avenue, Suite 2400
Austin, Texas 78701
(512) 536-3184

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